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#### **REMARKS**

Claims 1-25 are pending and claims 3-13 and 16-25 are under examination. Claims 4-6 and 19-25 have been canceled. Claims 3, 7, 9, 11-13, 16 and 17 have been amended. Applicants maintain that these amendments raise no issue of new matter and are fully supported by the specification as filed. Applicants respectfully request that this Amendment be entered. Upon entry of this Amendment, claims 1-3 and 7-18 will be pending and claims 3, 7-13 and 16-18 will be under examination.

#### **Title of the Invention**

The Examiner objected to the title of the invention as allegedly not descriptive. In response, applicants have amended the title to recite "RAGE-Related Methods for Treating Inflammation."

#### **Claim Objections**

The Examiner objected to claims 7, 9, 11-13 and 16-25 for allegedly reciting multiple inventions.

In response to the Examiner's objection to claims 19-25, but without conceding the correctness thereof, applicants point out that these claims have been canceled, thereby rendering the objection thereof moot.

In response to the Examiner's objection to claims 7, 9, 11, 13 and 16-18, but without conceding the correctness thereof, applicants

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point out that amended claims 7, 9, 11, 13 and 16-18 are only directed to one invention.

### **Drawings Objection**

The Examiner states that the Figures have been objected to by the draftsman as set forth in the Notice of Draftsman's Patent Drawing Review included as part of the Office Action. A copy of the Notice is attached hereto as Exhibit B.

In response, applicants have amended the application herein by replacing Figures 2, 3A, 3B, 5, 9, 11-16 and 18-22 with corrected Figures 2, 3A, 3B, 5, 9, 11-16 and 18-22.

Applicants maintain that the corrected Figures fully address the objections as set forth by the draftsman in the June 1, 2001 Notice of Draftsman's Patent Drawing Review.

### **Rejection under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claim 5 under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, the Examiner asserted that the term "a portion thereof" is not defined in the specification.

In response to the Examiner's rejection of claim 5, but without conceding the correctness thereof, applicants point out that this claim has been canceled, thereby rendering the rejection thereof moot.

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**Rejection under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 3-5 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserted that the disclosure in the specification does not provide an adequate written description of all possible agents or portion thereof of AGE or portion thereof of RAGE or portion thereof of sRAGE.

However, the Examiner did concede that the specification adequately discloses that the administration of sRAGE, V-domain of sRAGE or anti-RAGE antibody or anti-EN-RAGE F(ab'), fragment markedly attenuate inflammation.

In response to the rejection of claims 4 and 5, applicants point out that these claims have been cancelled, rendering the rejection thereof moot.

In response to the Examiner's rejection of claim 3, applicants respectfully traverse. Applicants point out that amended claim 3 does not recite all possible agents but rather specifically recites sRAGE, V-domain of sRAGE, or anti-RAGE antibody or anti-EN-RAGE F(ab'), fragment.

In view of the above remarks, applicants maintain that claim 3 satisfies the requirements of 35 U.S.C. §112, first paragraph.

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Further, the Examiner rejected claims 3-5 and 16-25 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Specifically, the Examiner asserted that the specification, while enabling for the administration of sRAGE, V-domain of sRAGE, or anti-RAGE antibody or anti-EN-RAGE F(ab'), fragment, does not reasonably provide enablement for all possible agents.

In response to the rejection of claims 4, 5 and 19-25, applicants point out that these claims have been cancelled, rendering the rejection thereof moot.

In response to the Examiner's rejection of claims 3 and 16-18, applicants respectfully traverse. Applicants point out that amended claims 3 and 16-18 do not recite all possible agents, but rather recite sRAGE, V-domain of sRAGE, or anti-RAGE antibody or anti-EN-RAGE F(ab'), fragment.

In view of the above remarks, applicants maintain that claims 3 and 16-18 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Further, the Examiner rejected claims 3-5 and 16-25 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Specifically, the Examiner asserted that the specification, while enabling for the binding of RAGE to either AGE or EN-RAGE, is not enabling for all ligands that bind RAGE.

In response to the rejection of claims 4, 5 and 19-25, applicants again point out that these claims have been cancelled, rendering the rejection thereof moot.

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In response to the Examiner's rejection of claims 3 and 16-18, applicants respectfully traverse. Applicants point out that amended claims 3 and 16-18 do not recite all possible ligands of RAGE, but rather recite AGE and EN-RAGE.

In view of the above remarks, applicants maintain that claims 3 and 16-18 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Further, the Examiner rejected claims 19-25 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Specifically, the Examiner asserted that the specification, while enabling for methods of treating delayed-type hypersensitivity, collagen-induced arthritis, rheumatoid arthritis and periodontal disease, is not enabling for the other recited diseases including, for example, colitis, asthma and diabetes.

In response to the rejection of claims 19-25, applicants point out that these claims have been cancelled, rendering the rejection thereof moot.

**Rejection under 35 U.S.C. §103(a)**

The Examiner rejected claims 3-11 under 35 U.S.C. §103(a) as allegedly obvious over United States Patent No. 5,864,018 ("Morser") in view of Ritthauer et al. (1995) ("Ritthauer").

Specifically, the Examiner asserts that it would have been prima facie obvious at the time of the invention to treat inflammation in a subject by inhibiting the interaction of AGE and RAGE by

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administering sRAGE or the anti-RAGE antibodies disclosed by Morser, because Morser demonstrates that sRAGE or anti-RAGE antibodies block the interaction between RAGE and its ligands and Ritthauer teaches that RAGE and its ligands are involved in the diseases involving inflammation.

In response to the Examiner's rejection of claims 4-6, but without conceding the correctness thereof, applicants point out that these claims have been canceled, thereby rendering the rejection thereof moot.

Further, applicants respectfully traverse the rejection of claims 3 and 7-11. In order to find the subject application obvious over Morser in view of Ritthauer, the prior art references, in combination, must teach or suggest all the elements thereof, and create both a motive to combine and a reasonable expectation of success. Morser and Ritthauer fail to do this.

Claims 3 and 7-11 provide a method for treating inflammation in a subject which comprises administering to the subject an agent selected from the group consisting of soluble receptor for advanced glycation endproduct (sRAGE), V-domain of sRAGE, or anti-RAGE antibody or anti-EN-RAGE F(ab')<sub>2</sub> fragment in an amount which inhibits the interaction between receptor for advanced glycation endproduct (RAGE) and either AGE or EN-RAGE, thereby treating inflammation in the subject.

This invention is based on the surprising discovery that inhibiting the interaction of RAGE and either AGE or EN-RAGE is useful in treating inflammation. Prior to the applicants' discovery, there

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was no reasonable expectation that inhibiting the interaction of RAGE and either AGE or EN-RAGE would succeed in treating inflammation. The Examiner's assertion of obviousness ignores this point.

The Examiner has in no way shown how Morser in view of Ritthauer teach or suggest applicants' invention which is based on this surprising finding. To maintain otherwise would constitute hindsight.

Moreover, the Examiner takes a position regarding obviousness that contradicts the Examiner's position regarding enablement. That is, the Examiner has stated on page 9 of the June 17, 2003 Office Action, that it would constitute undue experimentation to determine if a disease can be inhibited by inhibiting the interaction of RAGE and its ligand without conducting an experiment. The Examiner concedes that the instant specification is enabling for the treatment of diseases for which applicants have provided experimental data such as delayed-type hypersensitivity, collagen-induced arthritis, rheumatoid arthritis and periodontal disease. However, the Examiner indicates that the specification is not enabling for diseases such as colitis, asthma and diabetes where the applicants have not shown experimental data. Applicants maintain that the Examiner's position that experimental data are required to show operability of disease treatment renders untenable the Examiner's position that the claimed methods would nevertheless be expected to succeed absent such data.

Accordingly, applicants maintain that the subject claims are not obvious over Morser in view Ritthauer and therefore satisfy the



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requirements of 35 U.S.C. §103(a).

Further, the Examiner rejected claims 12, 13 and 16-25 under 35 U.S.C. §103(a) as allegedly obvious over Morser and Ritthauer in view of United States Patent No. 5,998,408 ("Baker").

Specifically, the Examiner asserts that it would have been prima facie obvious at the time of the invention to treat inflammation associated with autoimmune disease in a subject by inhibiting the interaction of AGE and RAGE by administering sRAGE or the anti-RAGE antibodies disclosed by Morser. This allegedly is because Morser demonstrates that sRAGE or anti-RAGE antibodies block the interaction between RAGE and its ligands, Ritthauer teaches that RAGE and its ligands are involved in the diseases involving inflammation and Baker teaches diseases involving inflammation, specifically the autoimmune process.

In response to the Examiner's rejection of claims 19-25, but without conceding the correctness thereof, applicants point out that these claims have been canceled, thereby rendering the rejection thereof moot.

Further, applicants respectfully traverse the rejection of claims 12, 13 and 16-18.

Claims 12, 13 and 16-18 are discussed above.

The non-obviousness of the rejected claims over Morser and Ritthauer is discussed above. Baker, which according to the

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Examiner merely teaches diseases involving inflammation, does not cure the deficiency of the other two references, it that it does not teach applicants' surprising discovery underlying the claimed invention.

Accordingly, applicants maintain that the subject claims are not obvious over Morser and Ritthauer in view of Baker and therefore satisfy the requirements of 35 U.S.C. §103(a).

#### **Obviousness-Type Double Patenting Rejection**

The Examiner provisionally rejected claims 3-11 and 16 as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 47, 50, 55-60, 62-65 and 67 of copending U.S. Application No. 09/167,705 in view of United States Patent No. 5,864,018 and Ritthauer et al. (1995). According to the Examiner, a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome a provisional rejection based on a nonstatutory double patenting ground.

In response, but without conceding the correctness of the Examiner's rejection, applicants will consider submitting a terminal disclaimer for claims 3-11 and 16 once the rejection is no longer provisional.

#### **Summary**

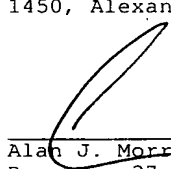
For the reasons set forth hereinabove, applicants respectfully request that all the claims of this application be allowed, and that the application proceed to issuance.

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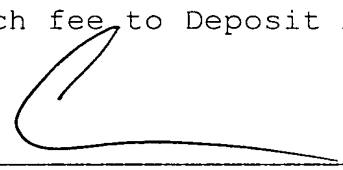
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

  
~~Alan J. Morrison~~  
Reg. No. 37,399

8/12/03  
Date

  
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07/872185

# NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 6-1-01 are:

A. ☐ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ☒ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be submitted according to the instructions on the back of this notice.

## 1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings:

Black ink. Color.

Color drawings are not acceptable until petition is granted.

Fig(s) \_\_\_\_\_

Pencil and non black ink not permitted. Fig(s) \_\_\_\_\_

## 2. PHOTOGRAPHS. 37 CFR 1.84(b)

1 full-tone set is required. Fig(s) \_\_\_\_\_

Photographs may not be mounted. 37 CFR 1.84(g)

☒ Poor quality (half-tone). Fig(s) 3, 4, 5, 21

## 3. TYPE OF PAPER. 37 CFR 1.84(e)

Paper not flexible, strong, white, and durable.

Fig(s) \_\_\_\_\_

☒ Erasures, alterations, overwritings, interlineations.

(folds, copy machine marks not accepted. Fig(s) 7

Mylar, vellum paper is not acceptable (too thin).

Fig(s) \_\_\_\_\_

## 4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:

21.0 cm by 29.7 cm (DIN size A4)

21.0 cm by 27.9 cm (8 1/2 x 11 inches)

All drawing sheets not the same size.

Sheet(s) \_\_\_\_\_

Drawings sheets not an acceptable size. Fig(s) \_\_\_\_\_

## 5. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm

SIZE: A4 Size

Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm

SIZE: 8 1/2 x 11

Margins not acceptable. Fig(s) \_\_\_\_\_

Top (T) \_\_\_\_\_

Left (L) \_\_\_\_\_

Right (R) \_\_\_\_\_

Bottom (B) \_\_\_\_\_

## 6. VIEWS. 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes.

Partial views. 37 CFR 1.84(h)(2)

Brackets needed to show figure as one entity.

Fig(s) \_\_\_\_\_

☒ Views not labeled separately or properly.

Fig(s) 11, 12, 13, 16, 18, 19, 21

Enlarged view not labeled separately or properly.

Fig(s) \_\_\_\_\_

## 7. SECTIONAL VIEWS. 37 CFR 1.84(i)

Hatching not indicated for sectional views. Fig(s) \_\_\_\_\_

Fig(s) \_\_\_\_\_

Sectional designation should be shown.

Fig(s) \_\_\_\_\_

Roman numbers. Fig(s) \_\_\_\_\_

## 8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)

Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) \_\_\_\_\_

## 9. SCALE. 37 CFR 1.84(k)

Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction.

Fig(s) \_\_\_\_\_

## 10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(i)

☒ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality).

Fig(s) 21, 20, 22

## 11. SHADING. 37 CFR 1.84(m)

Solid black areas pale. Fig(s) \_\_\_\_\_

Solid black shading not permitted. Fig(s) \_\_\_\_\_

Shade lines, pale, rough and blurred. Fig(s) \_\_\_\_\_

## 12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)

Numbers and reference characters not plain and legible.

Fig(s) \_\_\_\_\_

Figure legends are poor. Fig(s) \_\_\_\_\_

Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1)

Fig(s) \_\_\_\_\_

English alphabet not used. 37 CFR 1.84(p)(2)

Fig(s) \_\_\_\_\_

☒ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3)

Fig(s) 13, 21, 22

## 13. LEAD LINES. 37 CFR 1.84(q)

Lead lines cross each other. Fig(s) \_\_\_\_\_

Lead lines missing. Fig(s) \_\_\_\_\_

## 14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)

Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) \_\_\_\_\_

## 15. NUMBERING OF VIEWS. 37 CFR 1.84(u)

Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) \_\_\_\_\_

## 16. CORRECTIONS. 37 CFR 1.84(w)

Corrections not made from prior PTO-948 dated \_\_\_\_\_

## 17. DESIGN DRAWINGS. 37 CFR 1.152

Surface shading shown not appropriate. Fig(s) \_\_\_\_\_

Solid black shading not used for color contrast. Fig(s) \_\_\_\_\_

COMMENTS

REVIEWER

TELEPHONE NO.

ATTACHMENT



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**FIGURE 1**

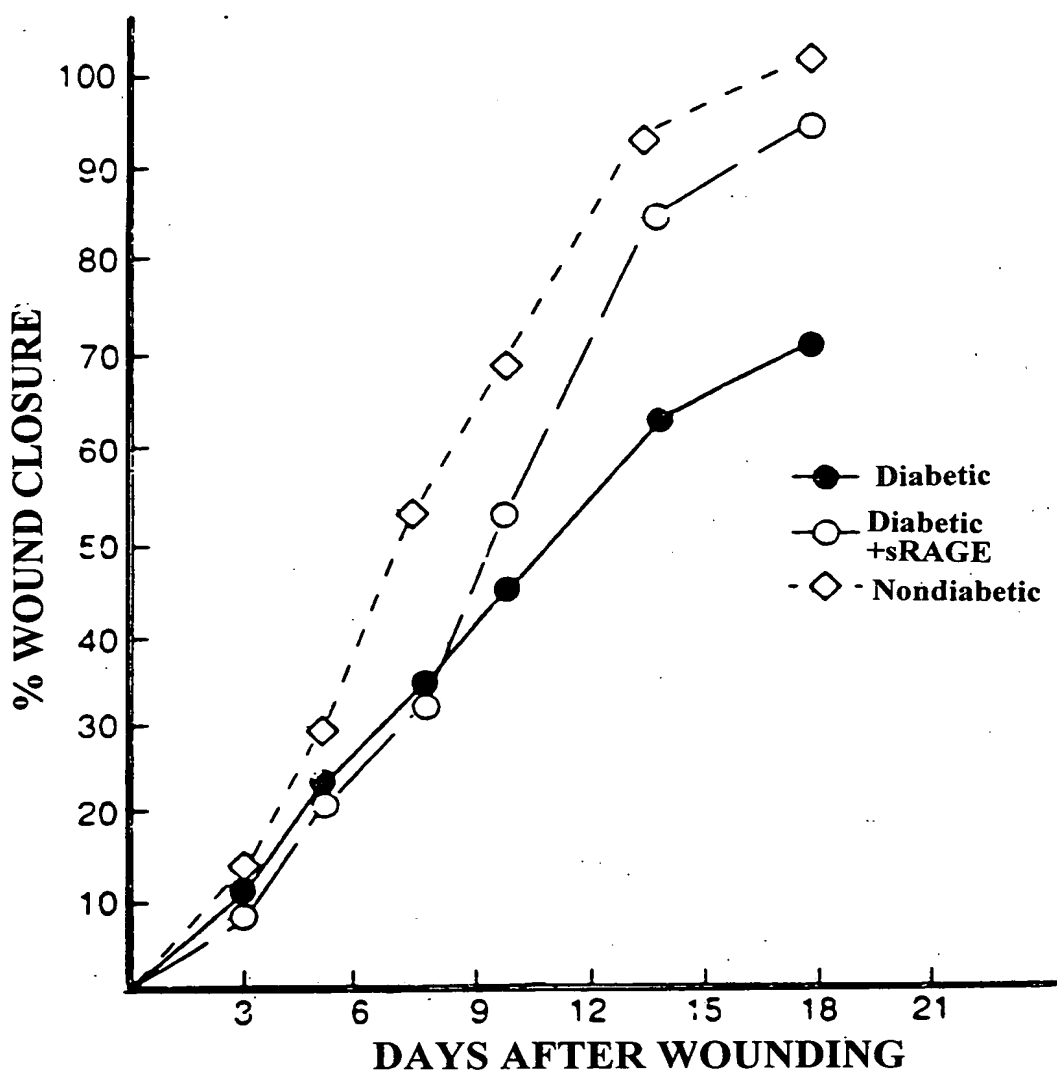
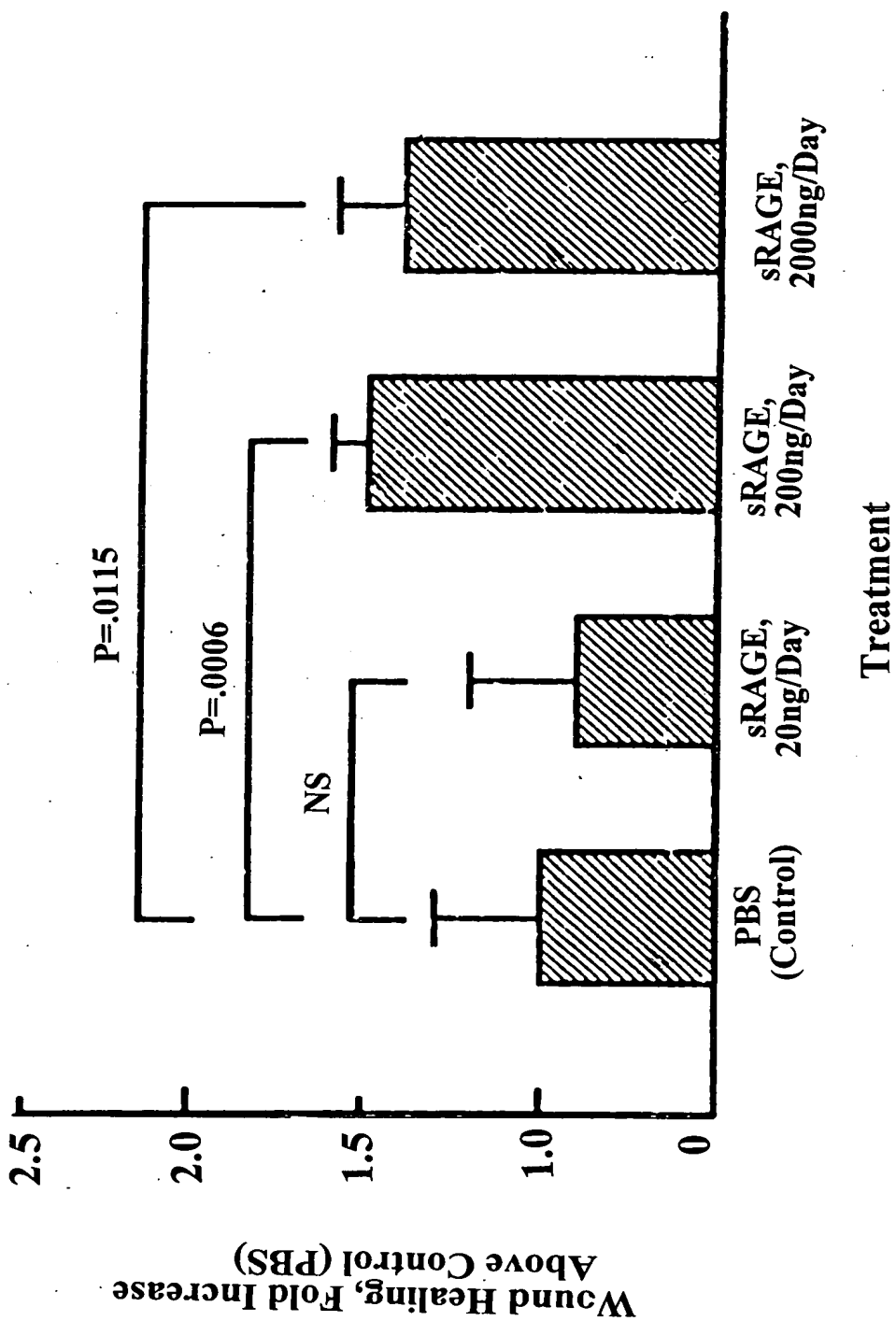


FIGURE 2



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Figure 3A

Figure 3B



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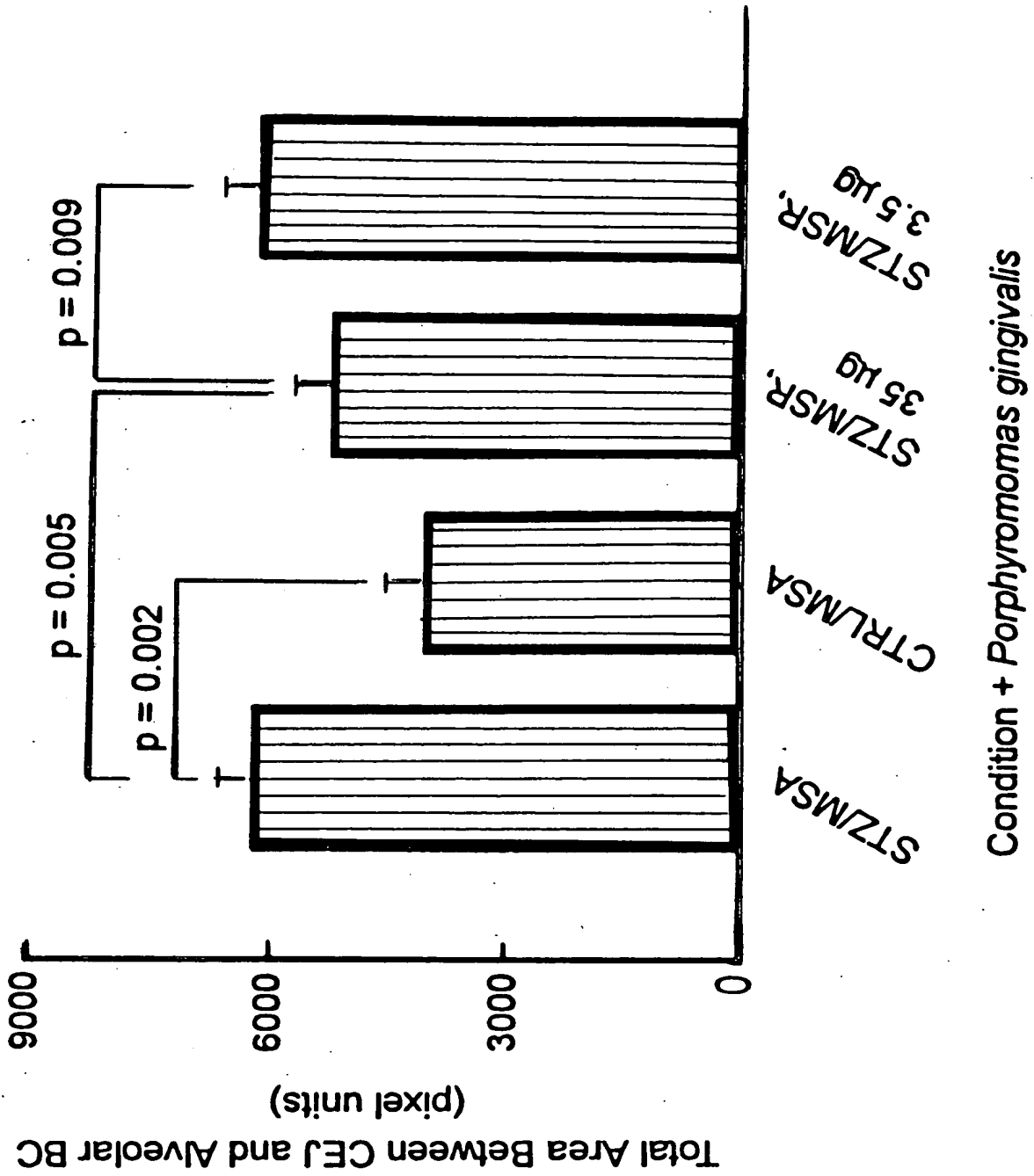


FIGURE 4



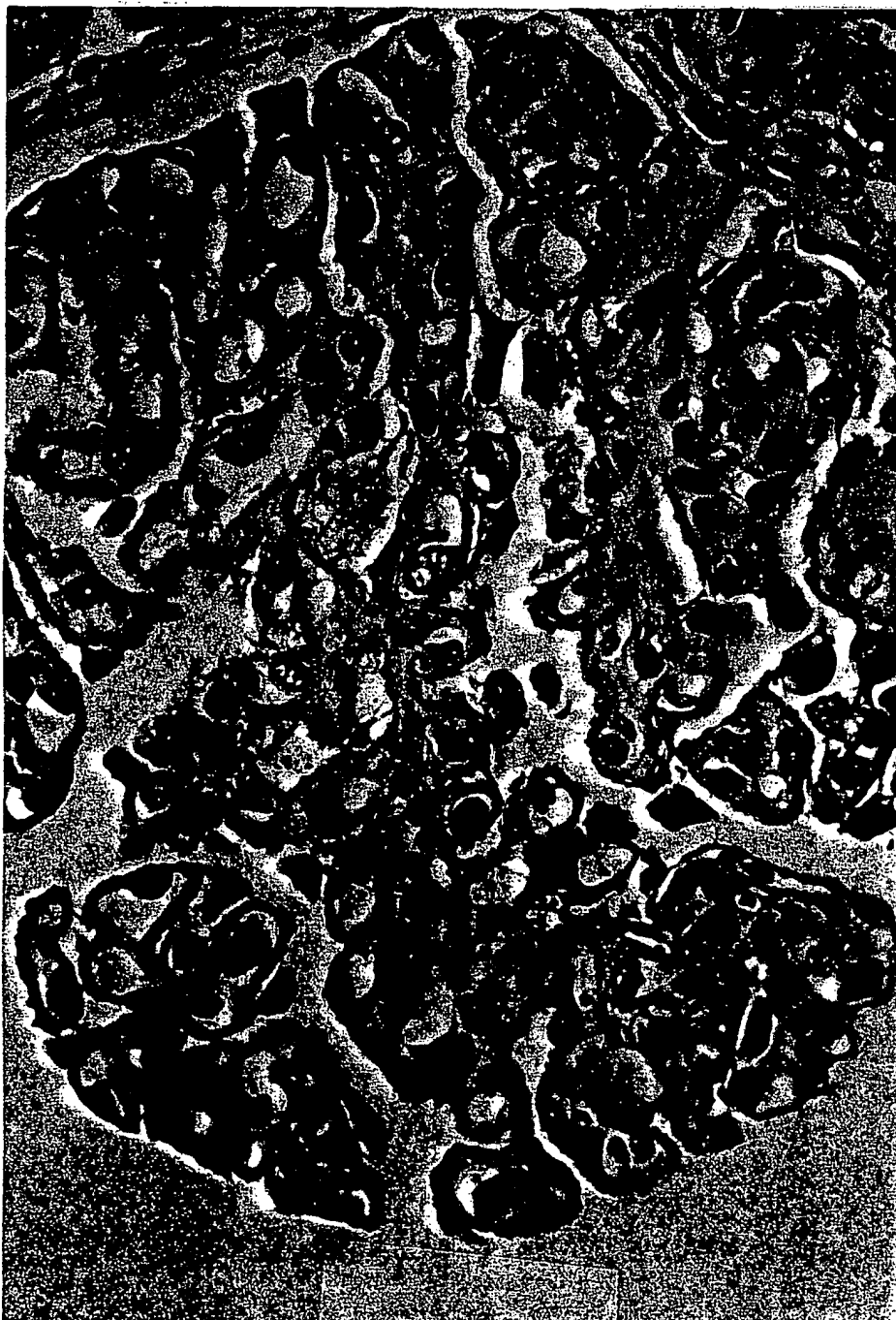


FIGURE 5

FIGURE 6

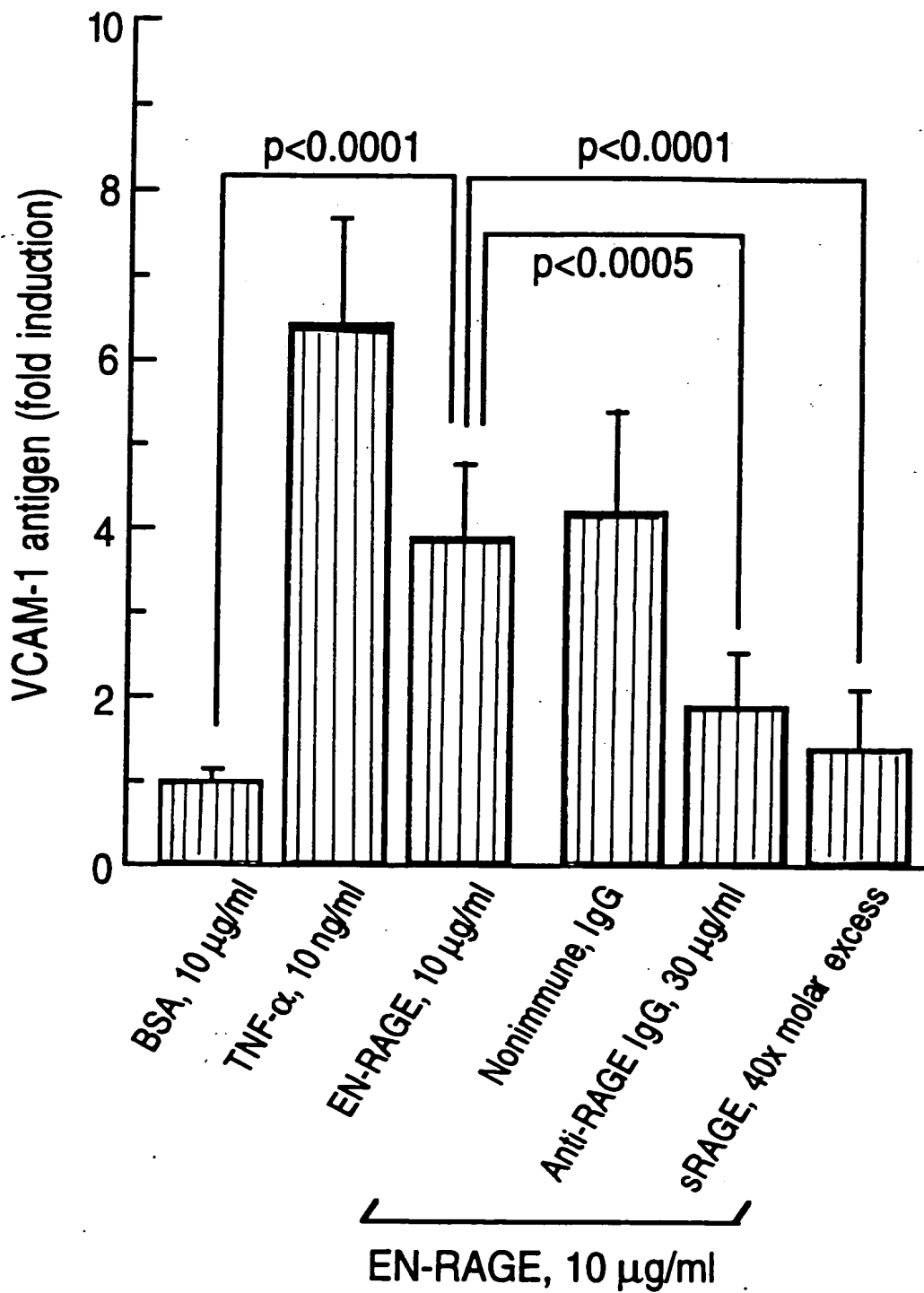


FIGURE 7

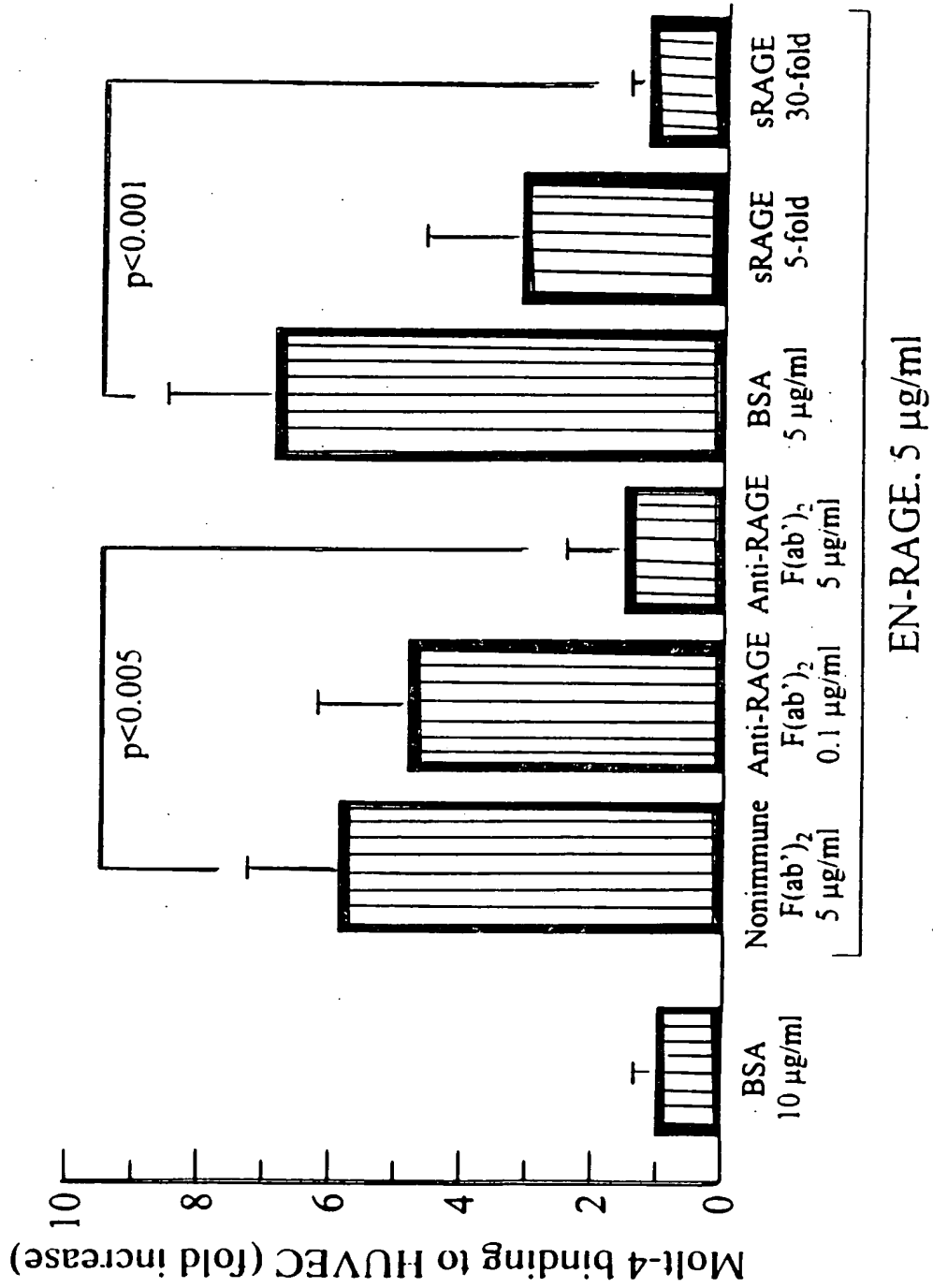
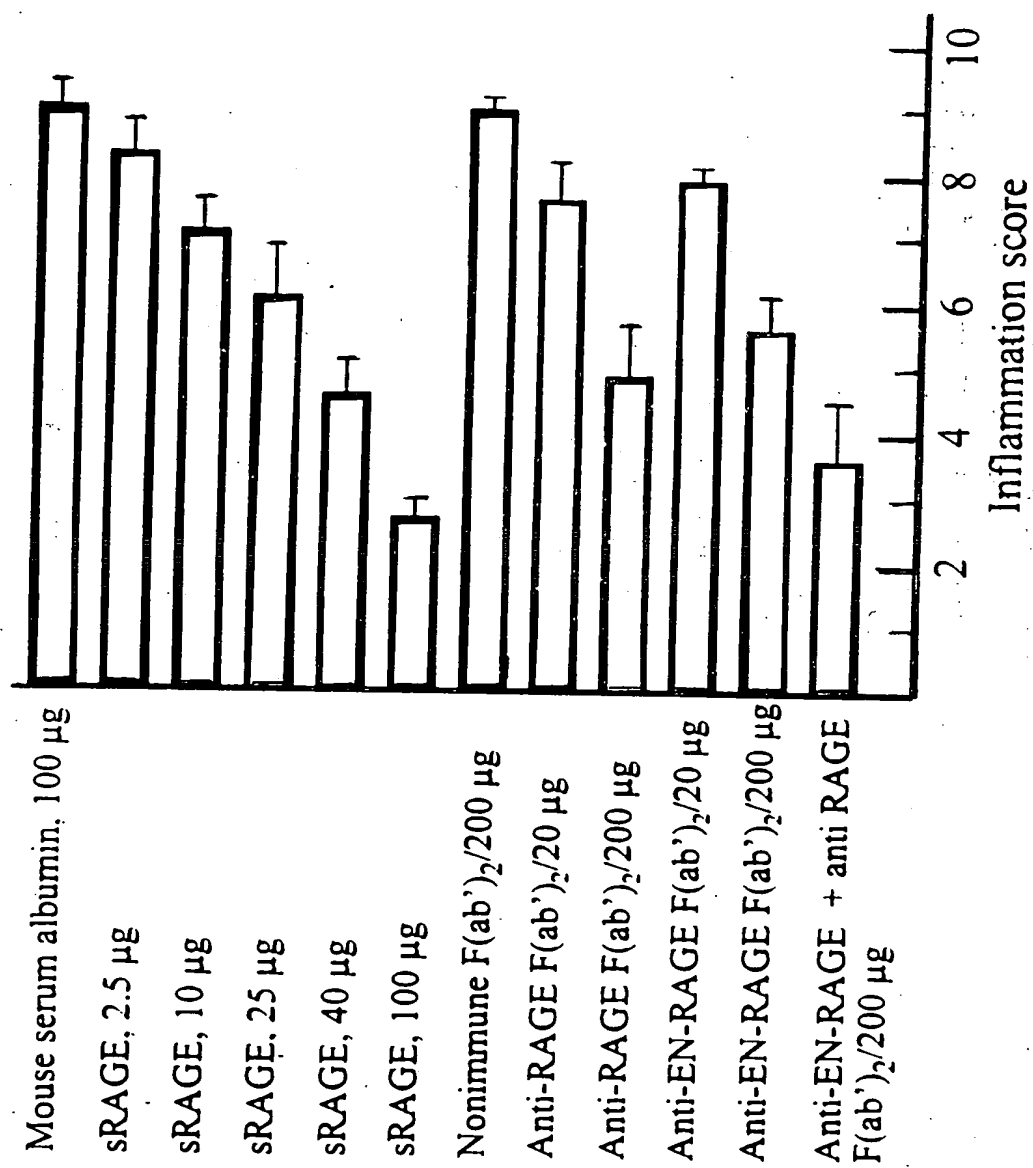
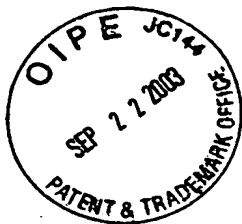


FIGURE 8





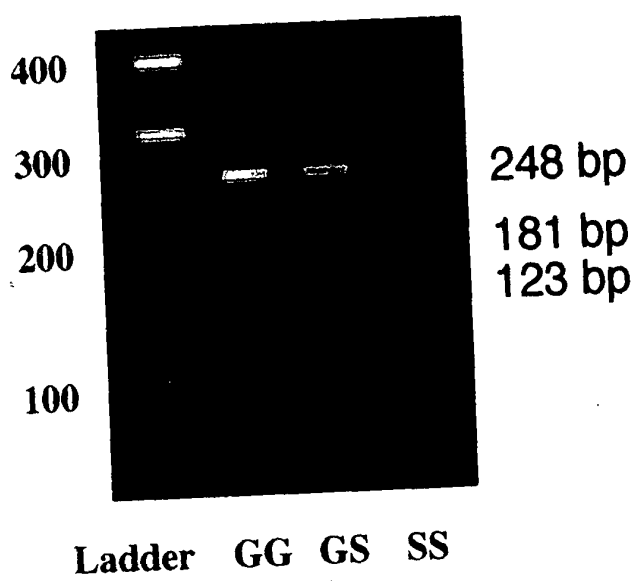
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FIGURE 9

ATGACTAAGCTGGAGGACCACTGGAGGGAATCATCAACATCTTC  
CACAGTACTCCGTTCCGGTGGGGCAATTTCGACACCTCAACAAG  
CGTGAGCTGAAGCAGCTGATCACAAAGGAACTTCCCAAACCCCT  
CCAGAACACCAAGACCAACCTACCATTGACAAATATTCCAAGA  
CCTGGATGCCGATAAGACGGAGCCGTCAGCTTTGAGGAATTCTGT  
AGTCCTGGTGTCCAGGTGCTGAAACAGCCACATAGATATCCA  
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CCTCCCTGAGGCTGCTCCCGAGGGAGAGAGAAATTATAAACGTAC  
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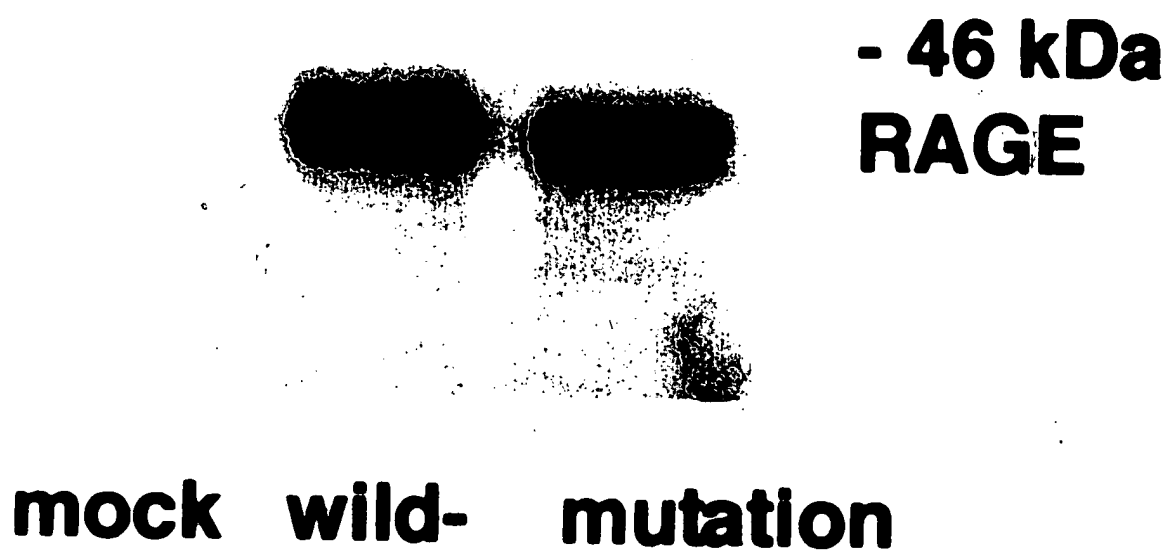
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**FIGURE 10**



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**FIGURE 11A**



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FIGURE 11B

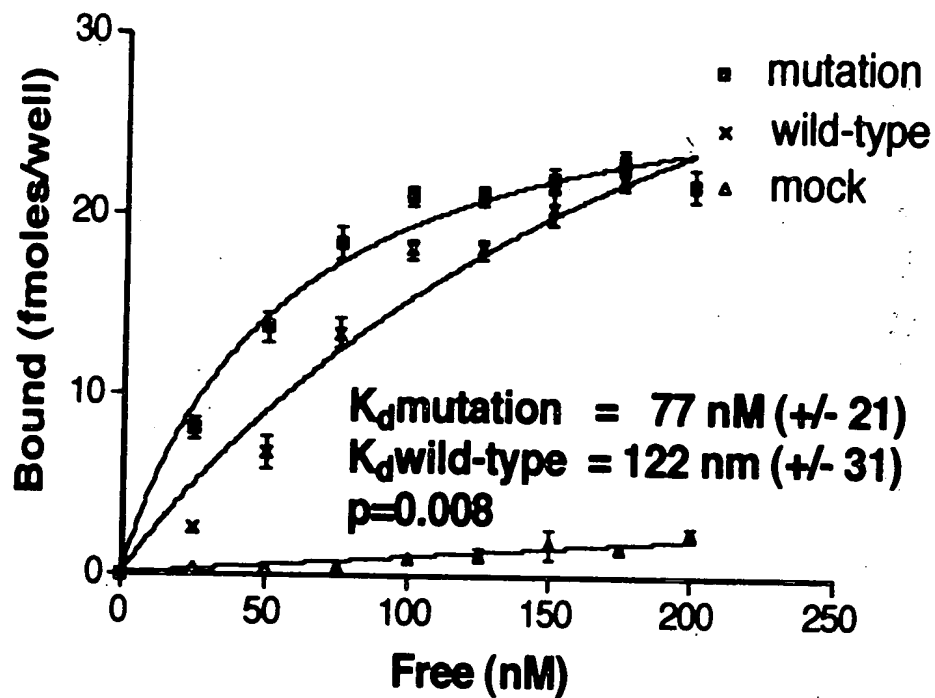
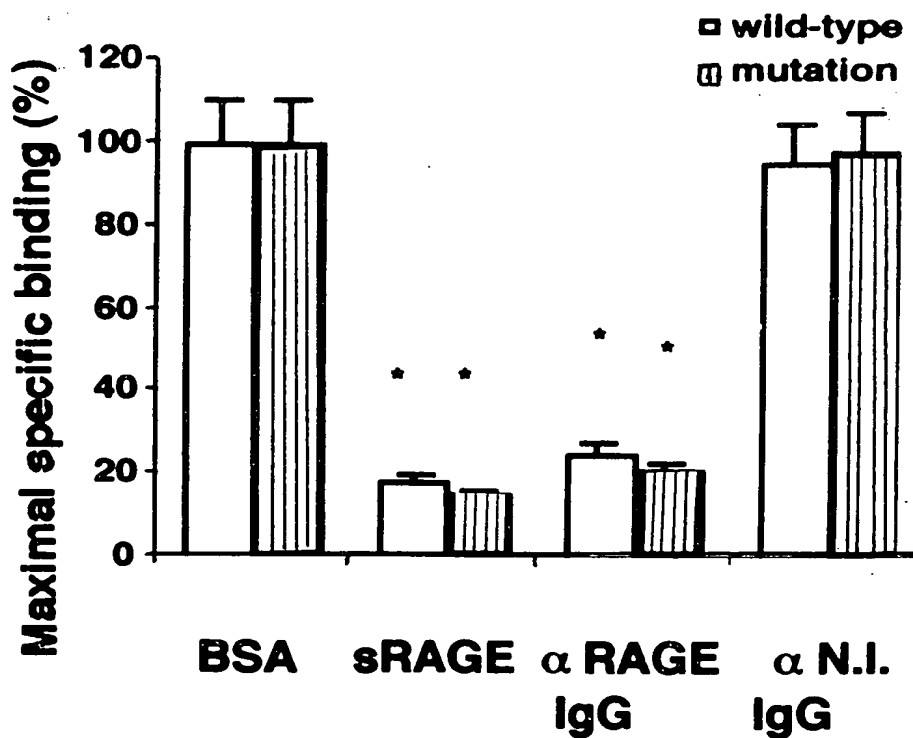


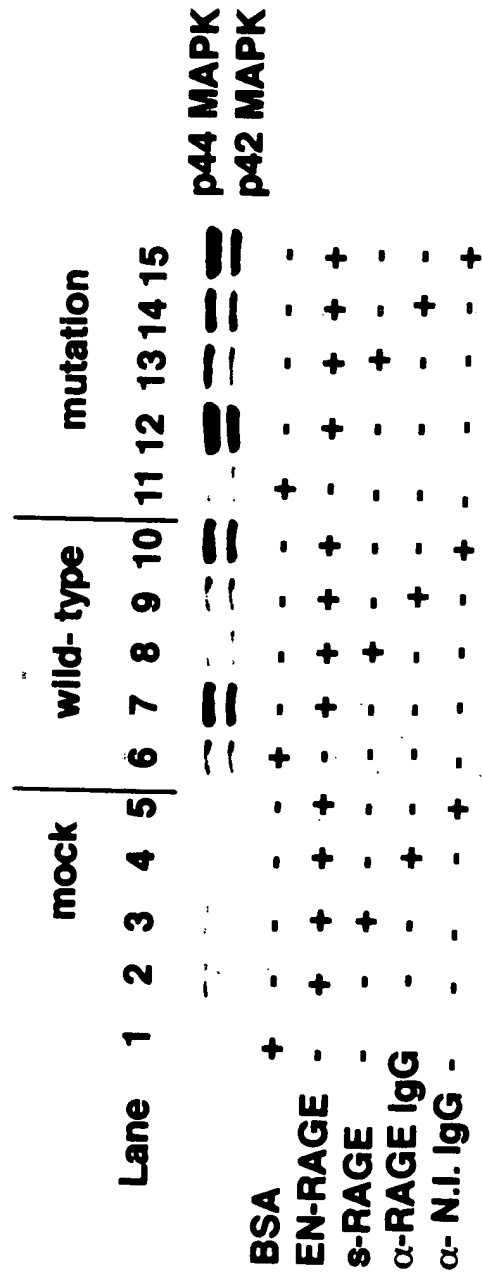
FIGURE 11C





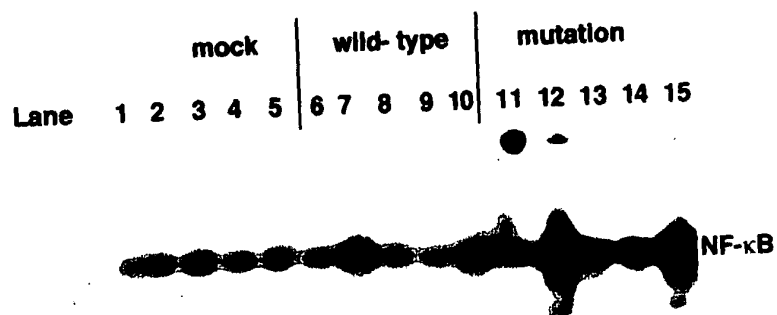
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FIGURE 11D



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FIGURE 11E



BSA	+	-	-	-	-	+	-	-	-	-	+	-	-	-	-
EN-RAGE-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+
α-RAGE	-	-	+	-	-	-	-	+	-	-	-	-	+	-	-
α-RAGE IgG-	-	-	+	-	-	-	-	-	+	-	-	-	-	+	-
α-N.I IgG-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	+

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FIGURE 12A

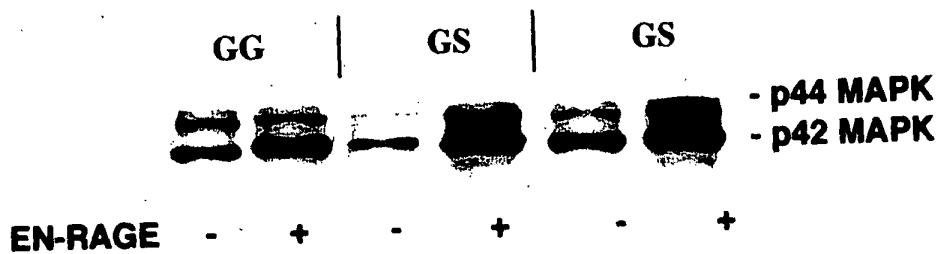


FIGURE 12B

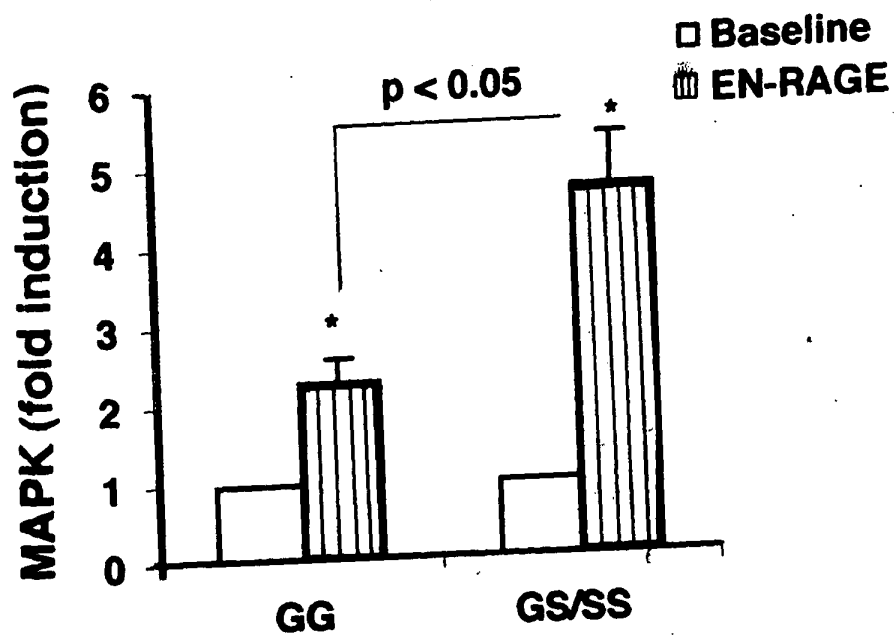


FIGURE 12C

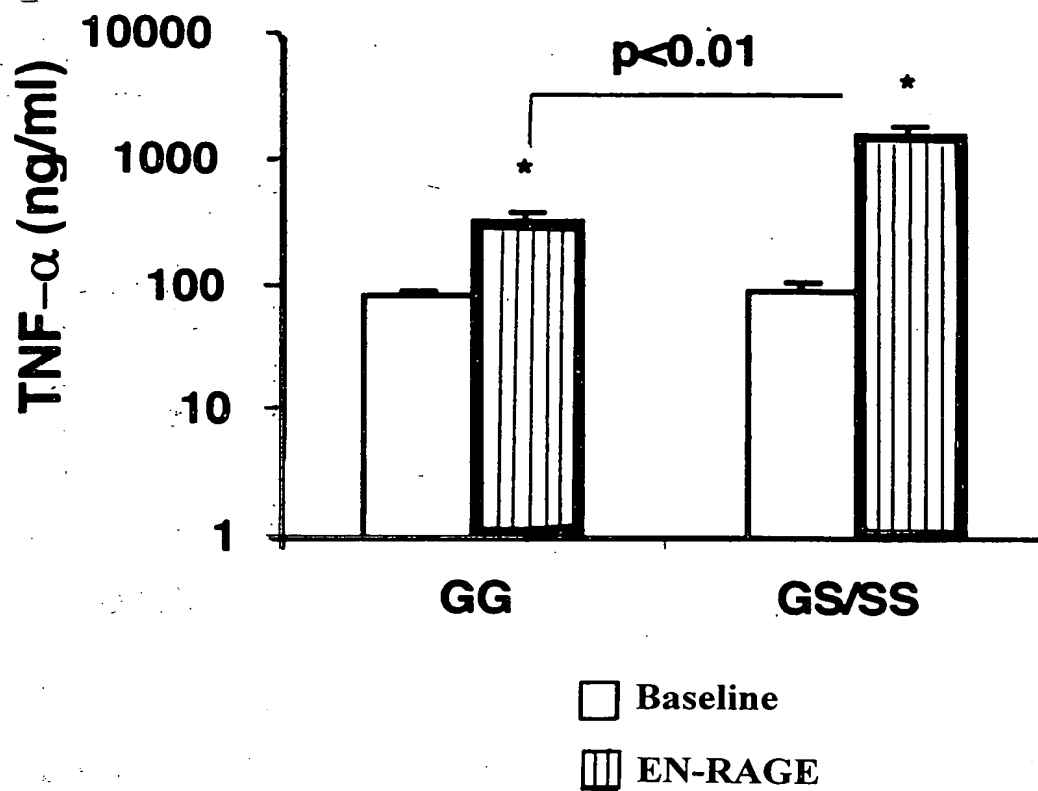
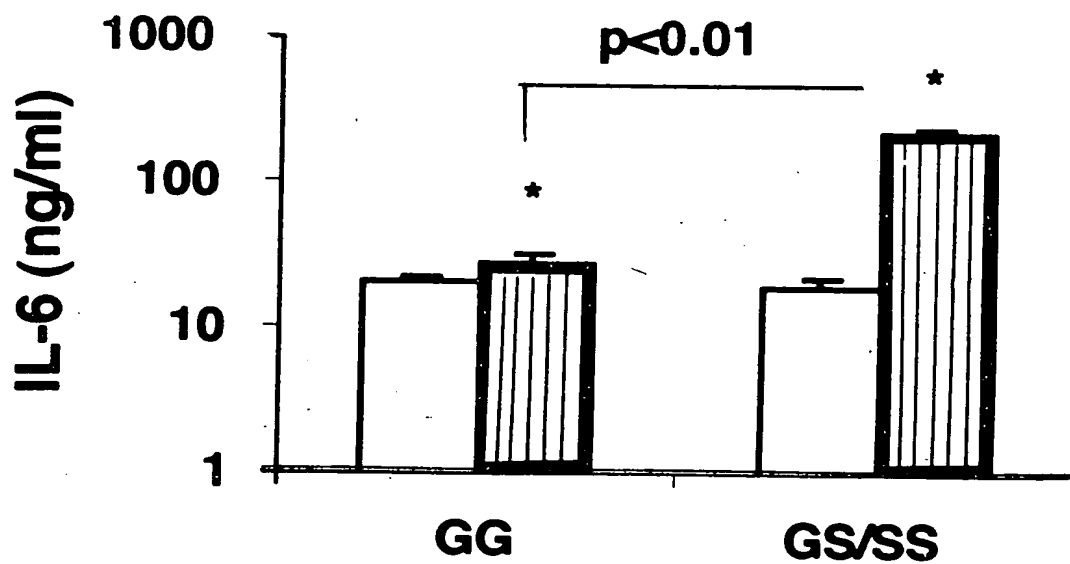


FIGURE 12D



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FIGURE 12E

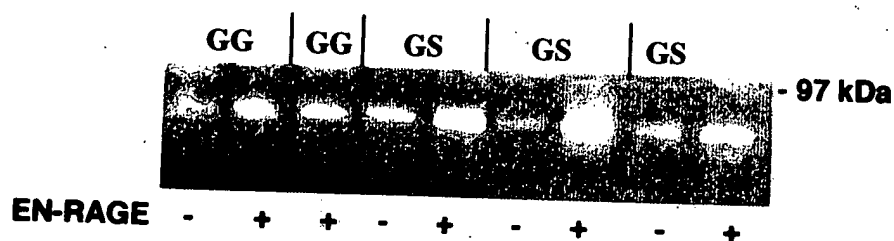
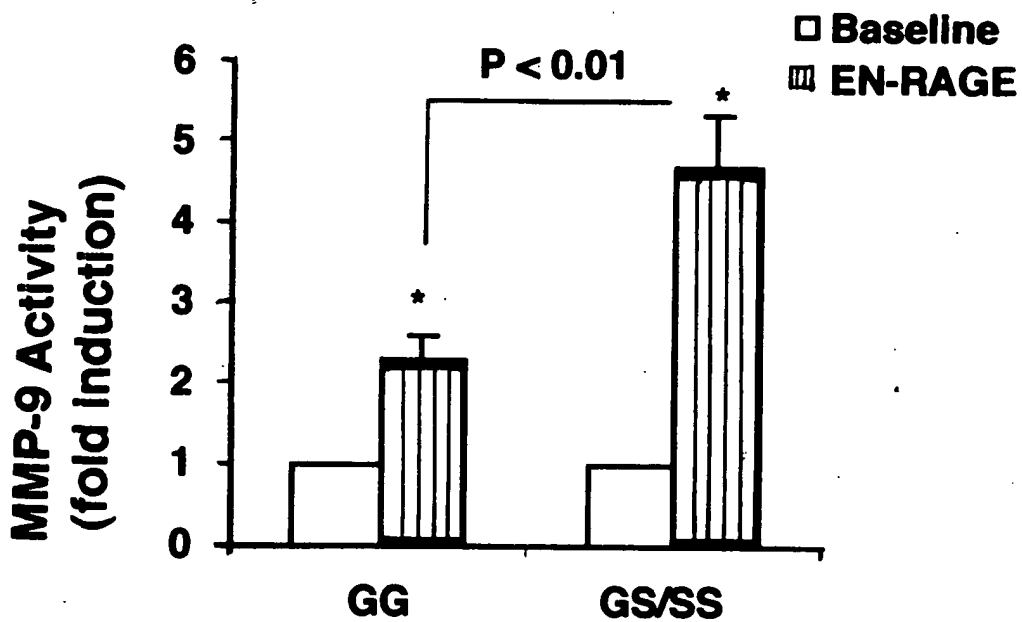
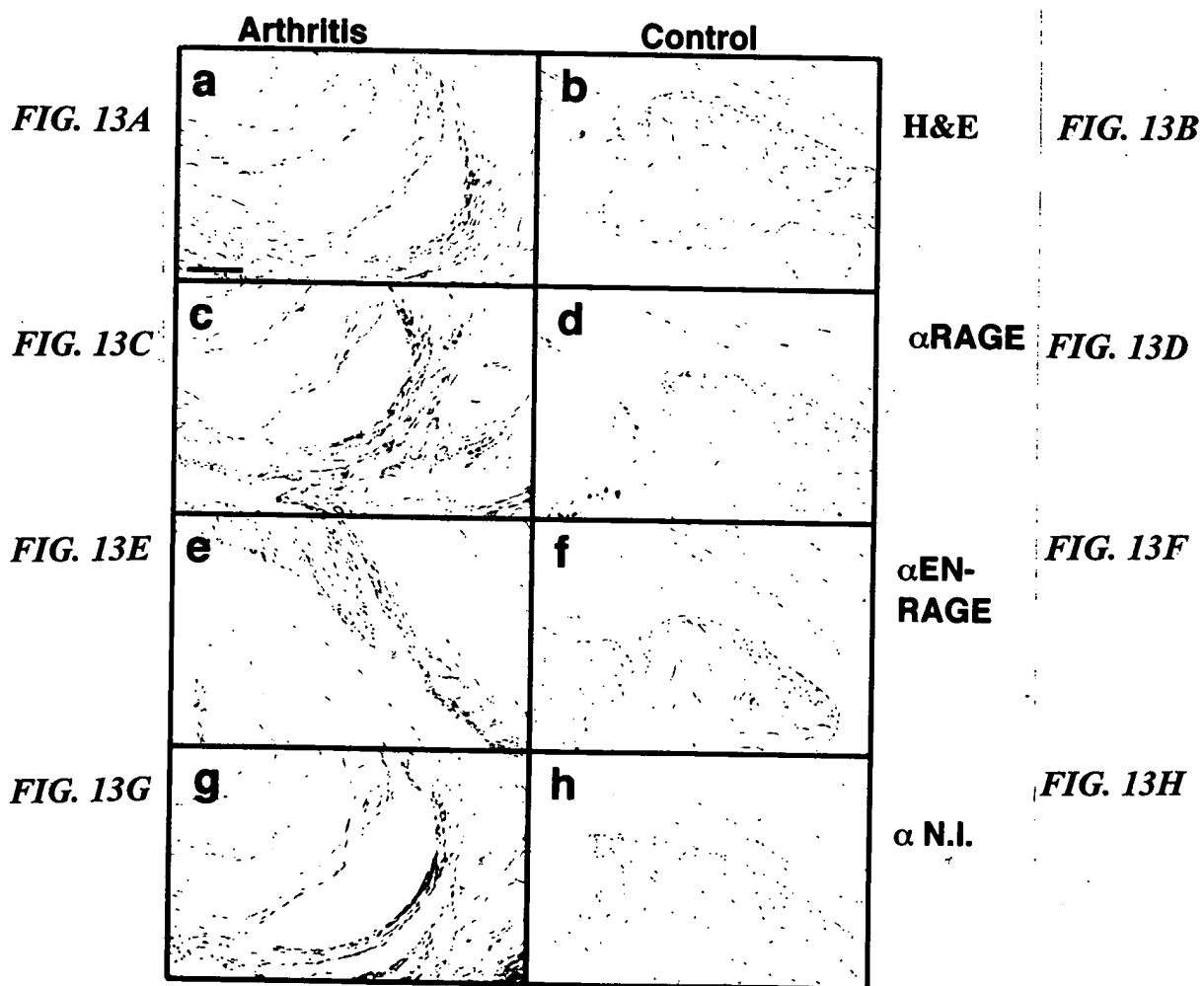


FIGURE 12F





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FIGURE 13I

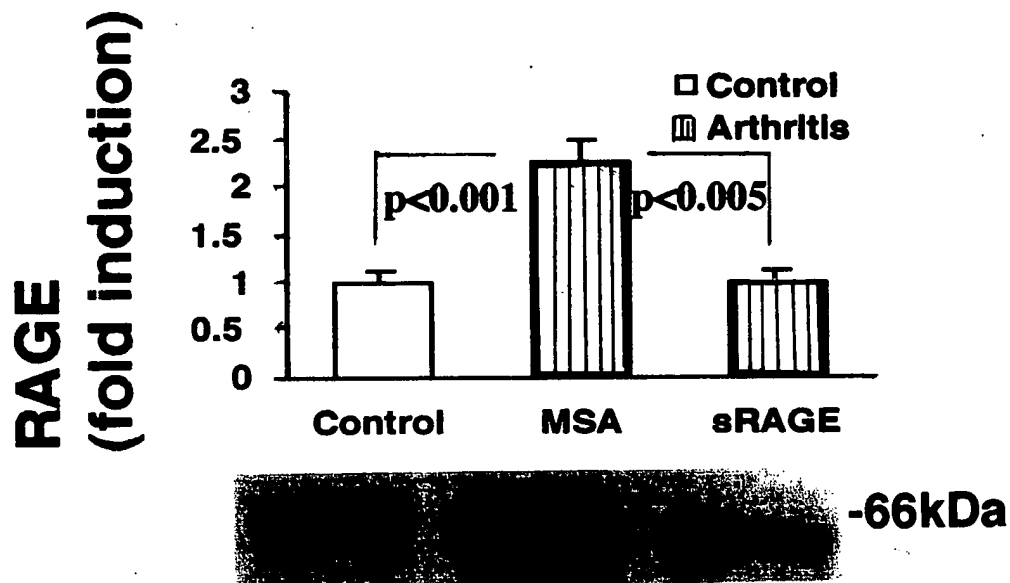


FIGURE 13J

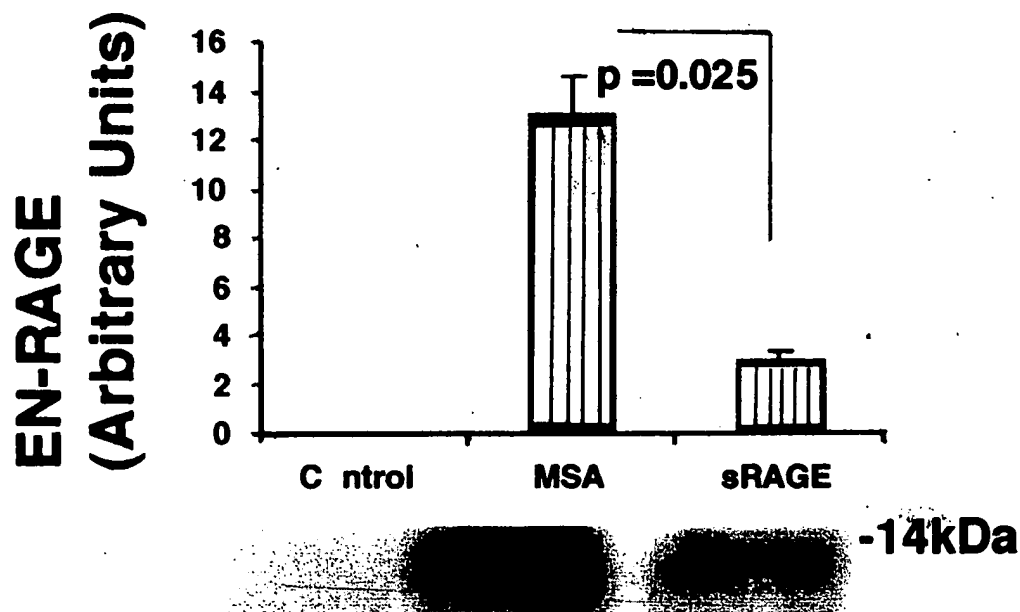


FIGURE 14B

0=no redness, swelling  
1=slight redness, swelling  
2=severe redness, swelling

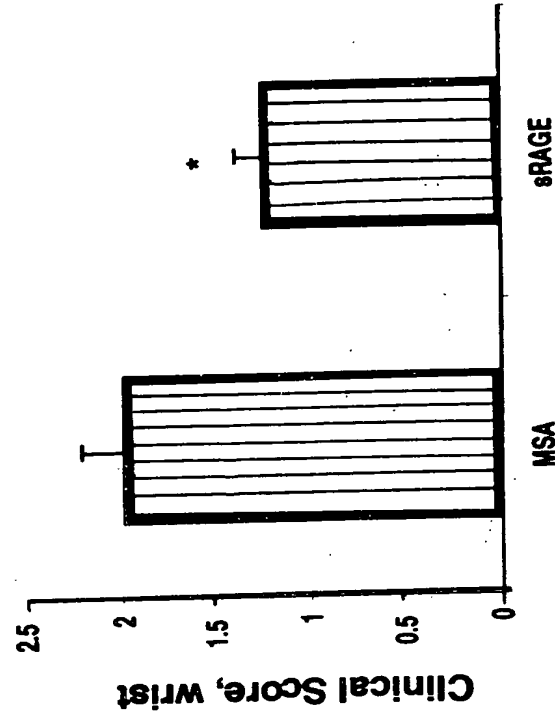
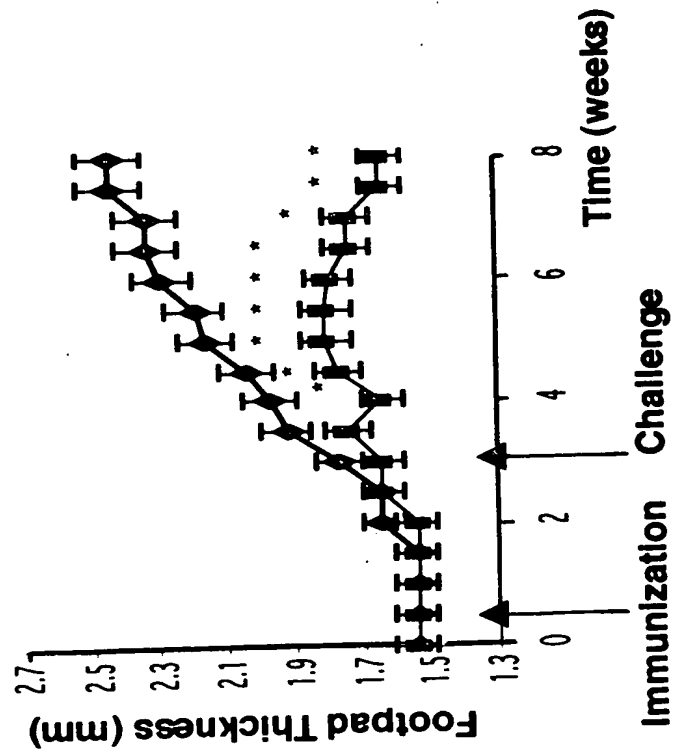


FIGURE 14A

◆ MSA  
■ sRAGE





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FIGURE 14C

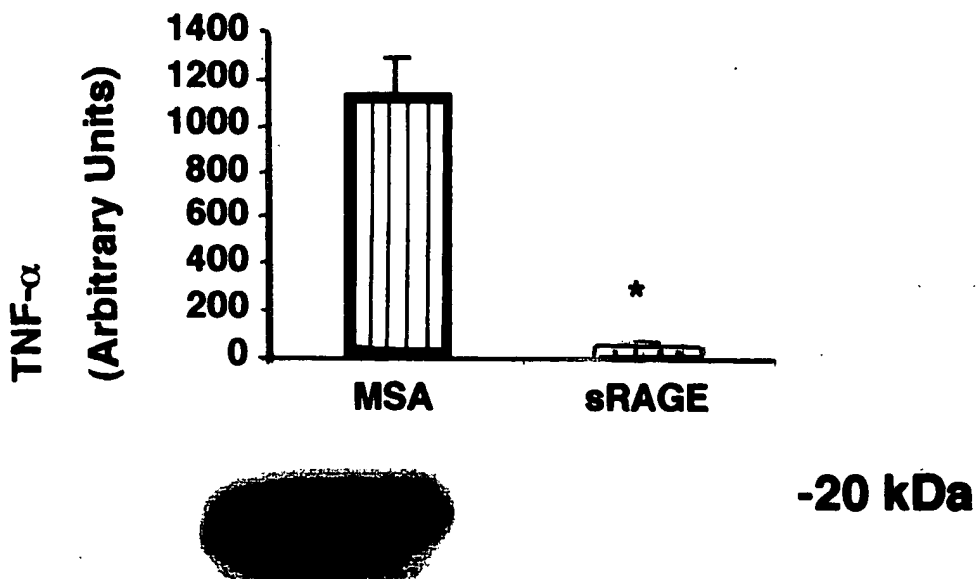
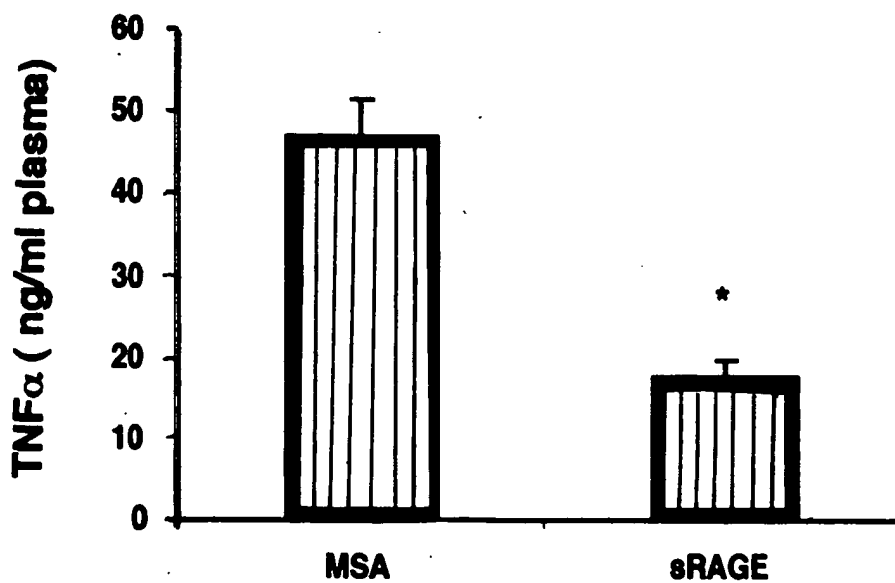


FIGURE 14D



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FIGURE 14F

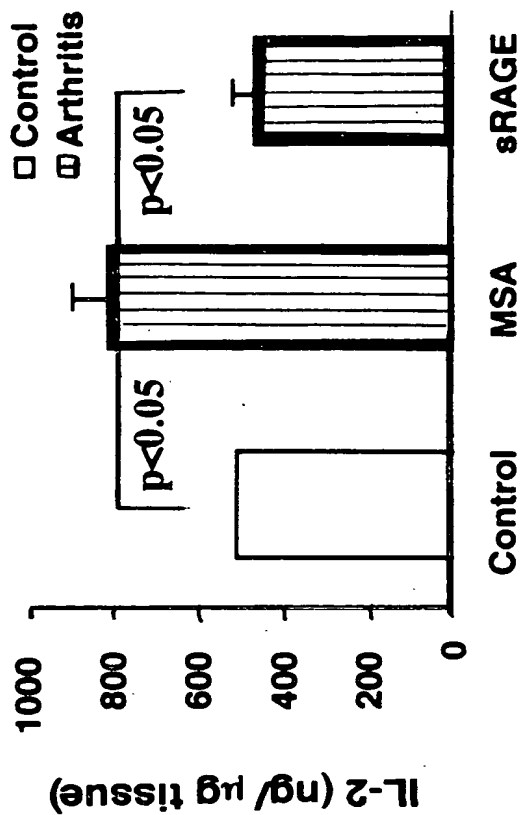
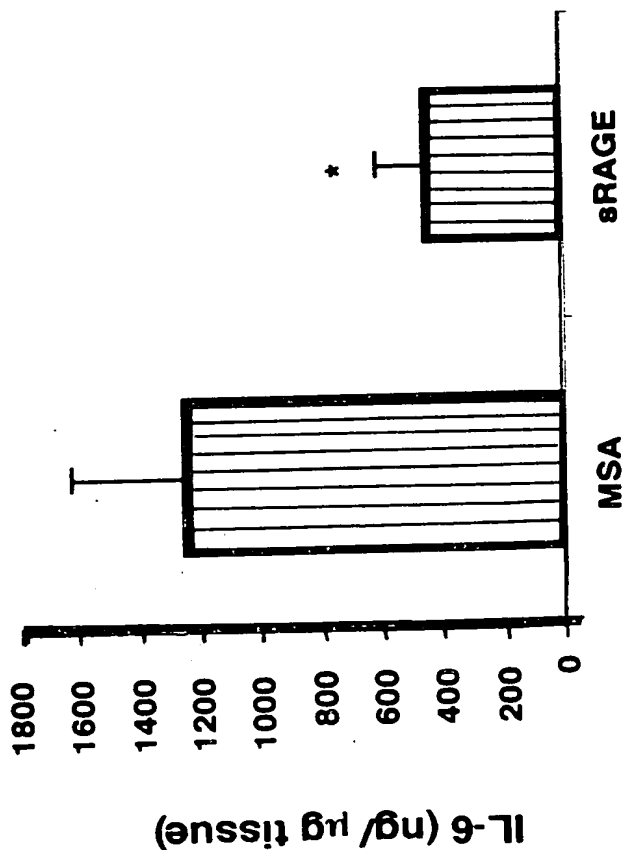
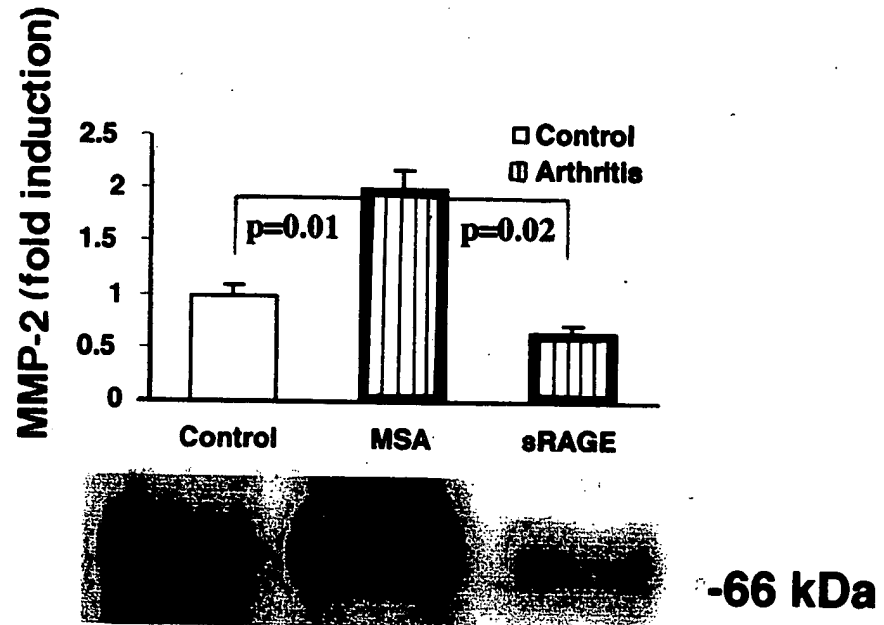


FIGURE 14E

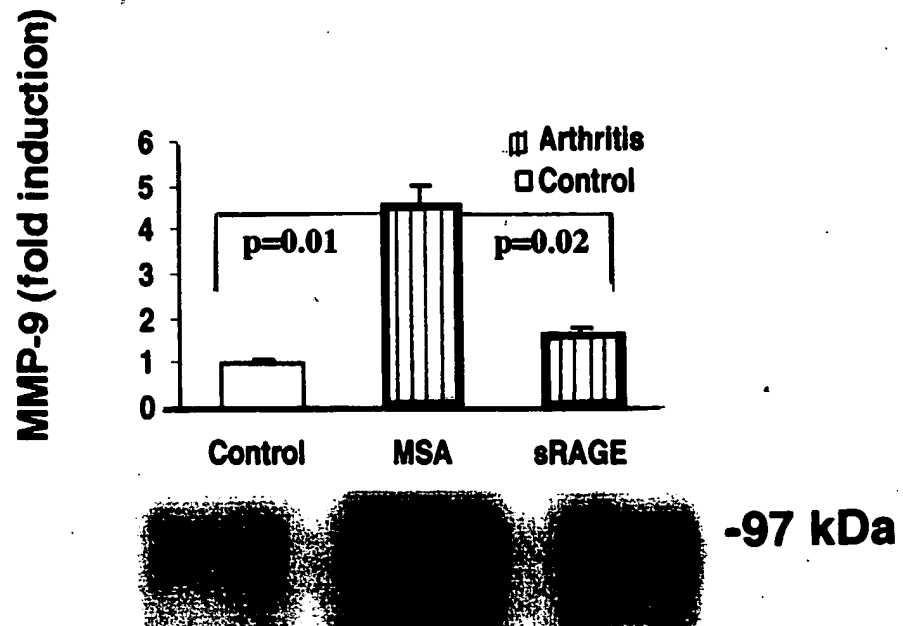


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**FIGURE 15A**



**FIGURE 15B**



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FIGURE 15C

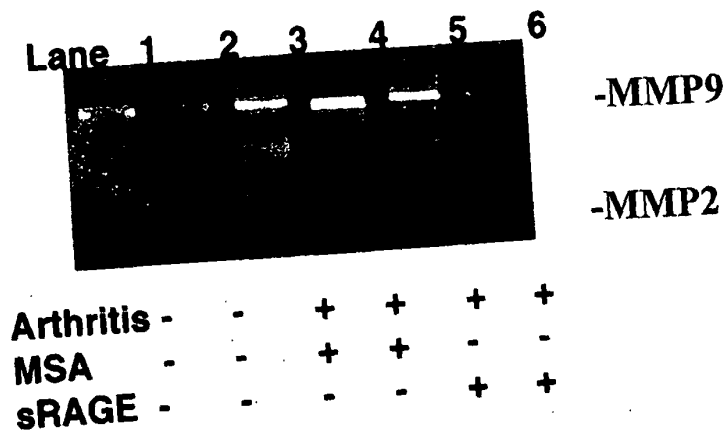
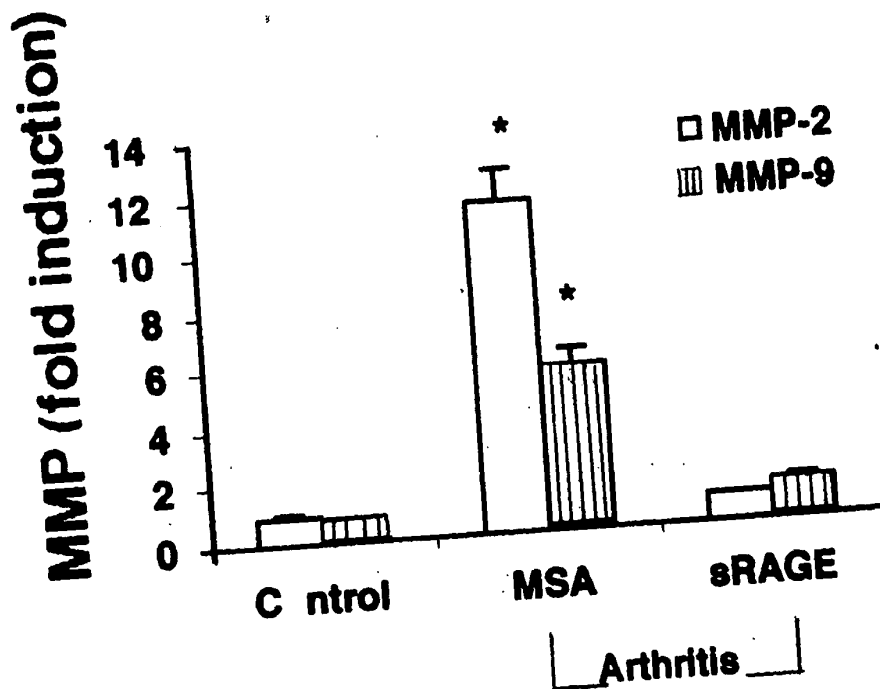


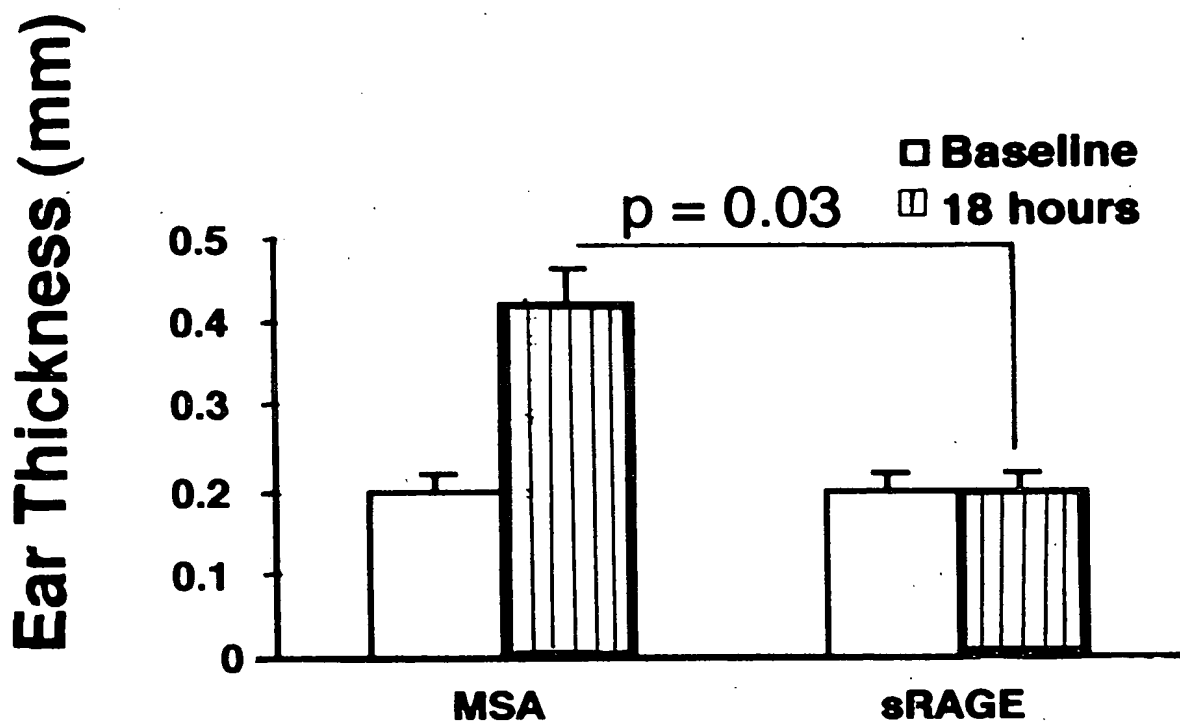
FIGURE 15D





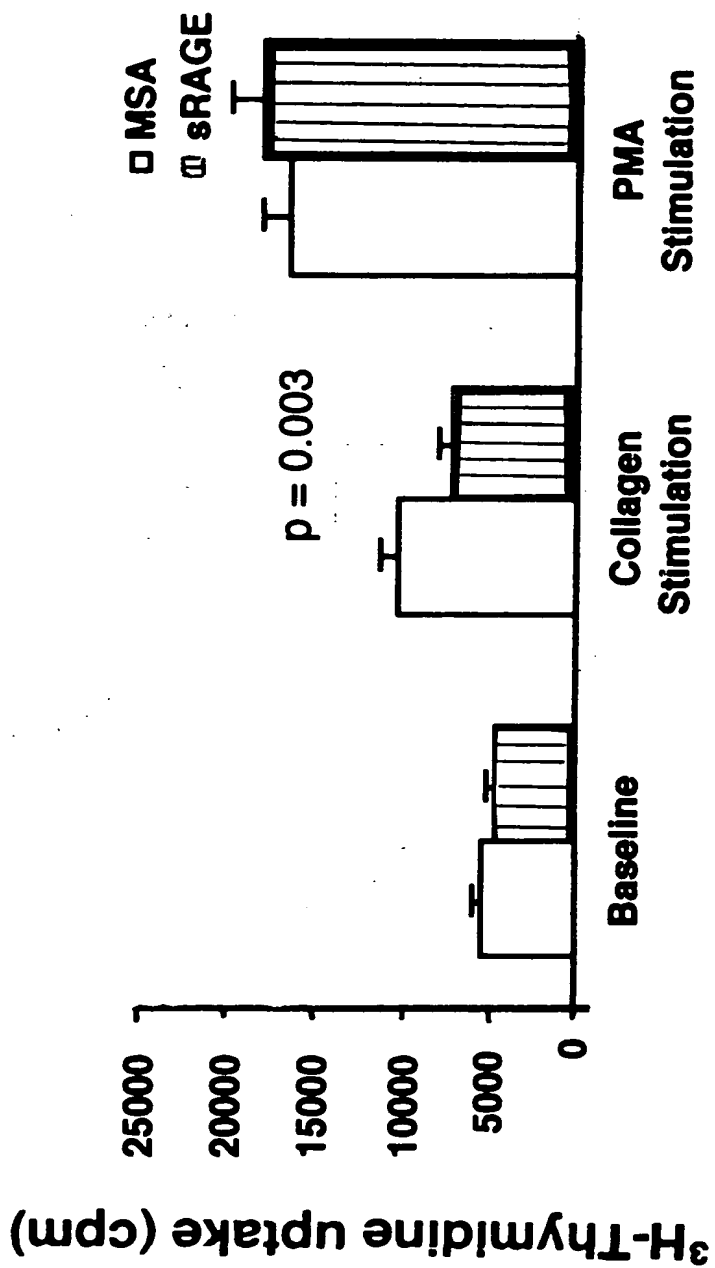
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*FIGURE 16A*



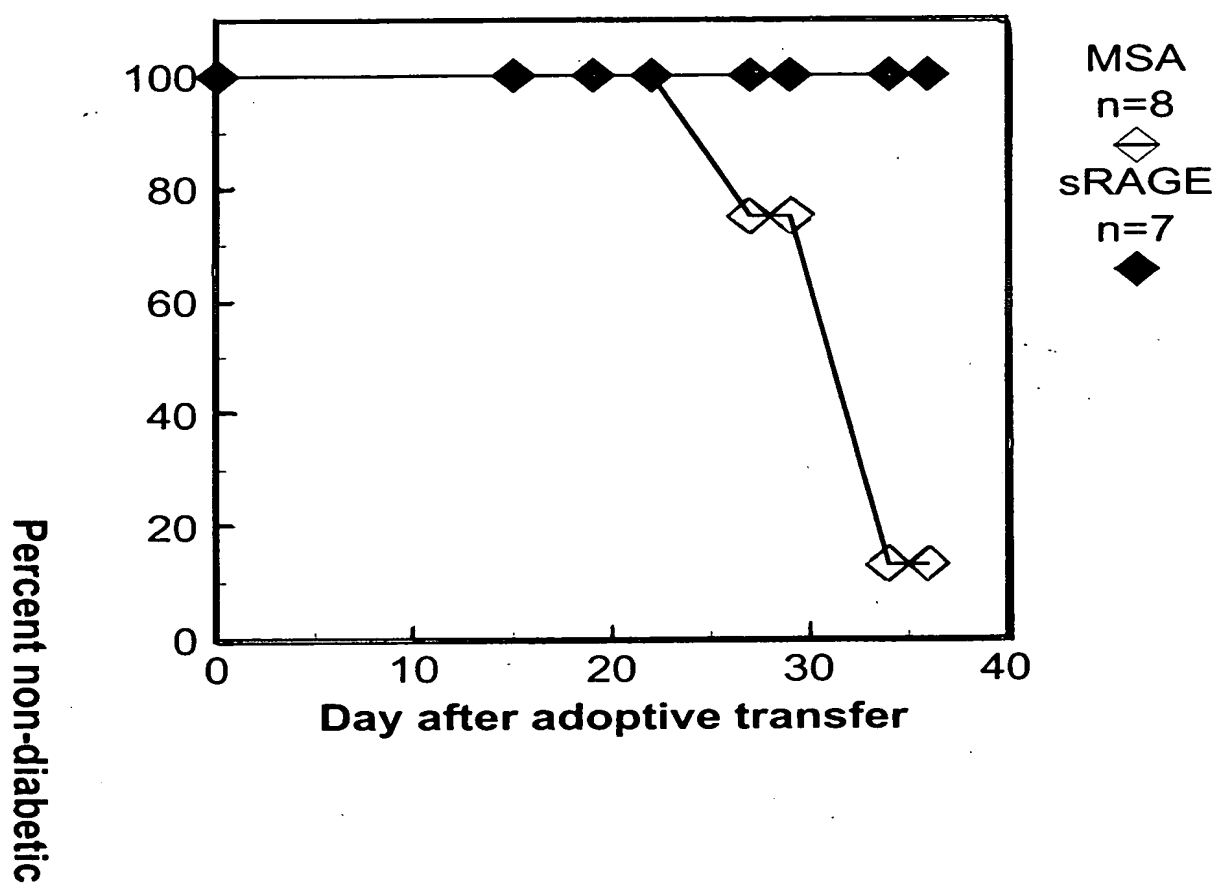
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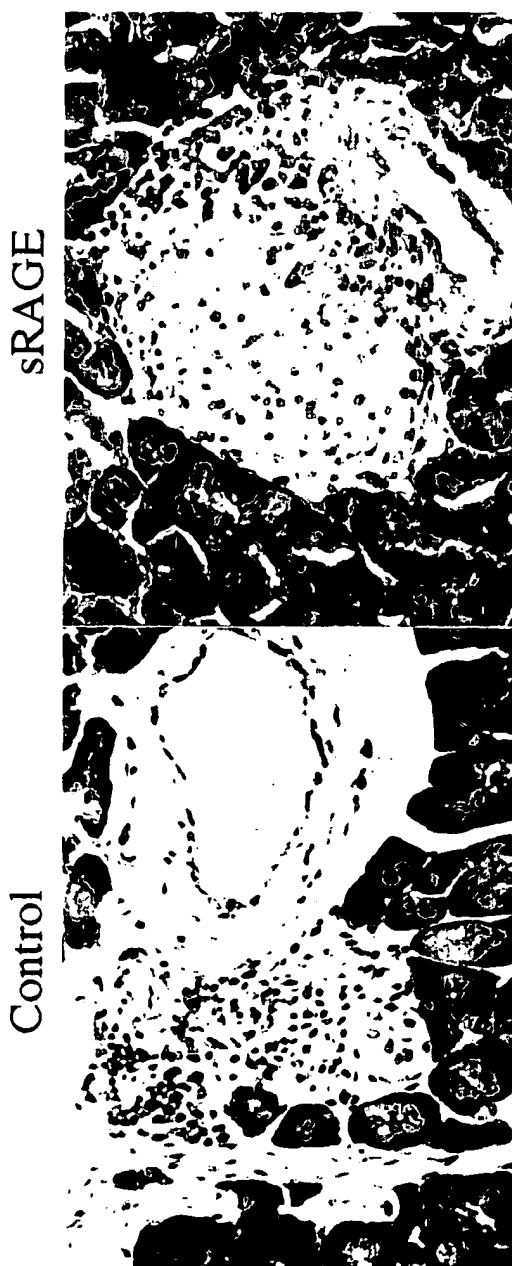
FIGURE 16B



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FIGURE 17



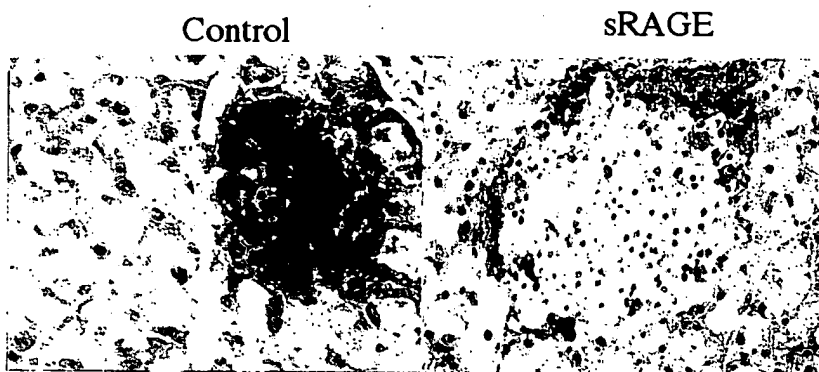
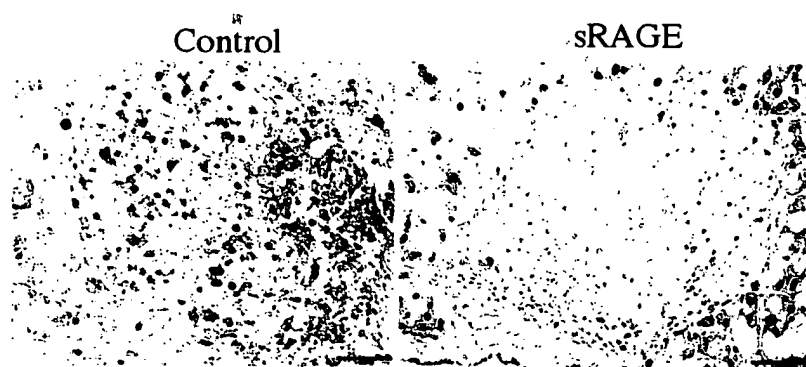


**FIGURE 18**



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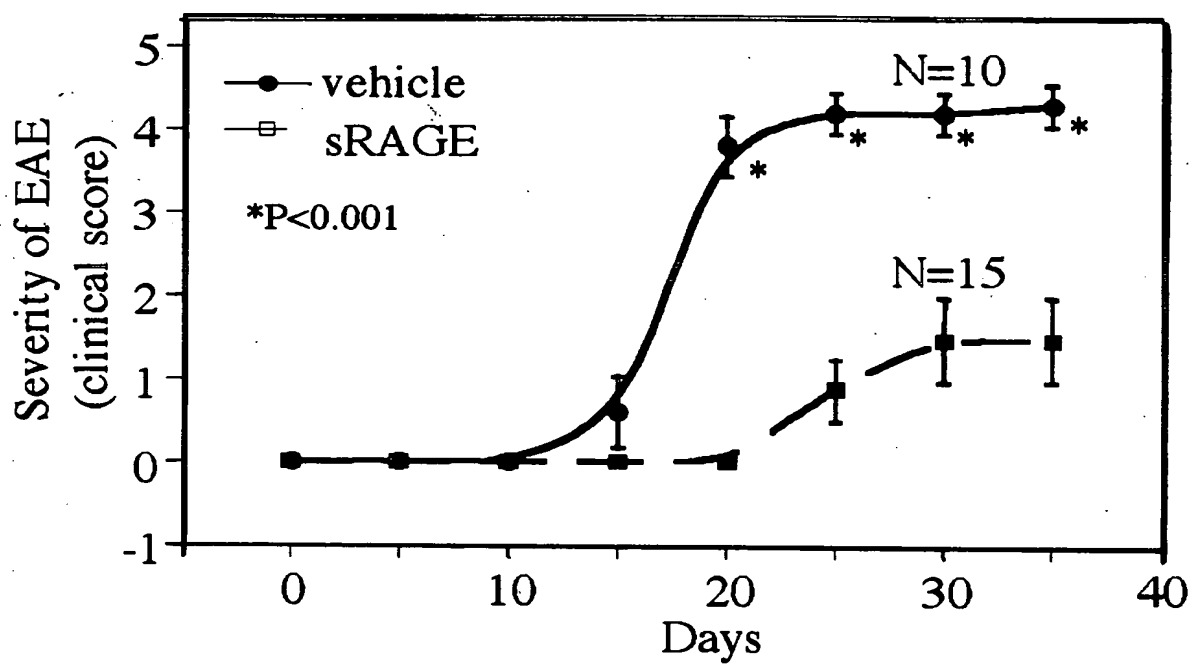
**FIGURE 19A**



**FIGURE 19B**

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**FIGURE 20**



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FIGURE 21D

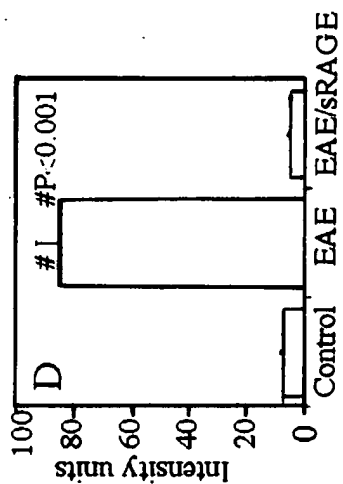


FIGURE 21C



FIGURE 21B



FIGURE 21A



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FIGURE 22

